

CLAIMS

1. A method of treating a patient suffering from a hyperproliferative disorder or photoageing, which method comprises lowering the endogenous level or activity of retinoic acid (RA) in a cell of the patient.
- 5 2. The method of claim 1, wherein the endogenous level of retinoic acid is lowered in a hyperproliferating cell or a cell suffering from photoageing of said patient.
- 3 The method of claim 1, wherein the endogenous level of retinoic acid in the cell is lowered to an extent that cell proliferation is reduced or abolished, and/or to an extent that cell differentiation is activated or enhanced.
- 10 4. The method of claim 1, wherein the method comprises inhibiting the uptake of retinol by a retinol binding protein receptor (RBPr).
5. The method of claim 1, wherein the method comprises antagonising one or more elements of a pathway which leads to biosynthesis of retinoic acid.
6. The method of claim 5, wherein the method comprises antagonising a retinol
15 dehydrogenase (RDH), an alcohol dehydrogenase (ADH), or a retinal dehydrogenase (RaldH).
7. The method of claim 6, wherein the method comprises antagonising a retinol dehydrogenase enzyme selected from the group consisting of: RoDH1, RoDH2, RoDH3, RoDH4, CRAD1, CRAD2, RDH5 and retSDR1, or an alcohol dehydrogenase selected from
20 the group consisting of: ADH1, ADH2 and ADH4, or a retinal dehydrogenase enzyme selected from the group consisting of: ALDH1, ALDH6, RALDH2 and ALDH-t.

8. The method of claim 1, wherein the antagonist of the retinol binding protein receptor is selected from the group consisting of:

- (a) an immunoglobulin capable of binding to retinol binding protein receptor;
- (b) a peptide comprising a sequence from a receptor binding region of retinol binding protein;
- (c) a peptide comprising a sequence K29 - Q38, G59 - A71 or M88 - D102 of retinol binding protein;
- (d) a peptide comprising a heterodimer consisting of peptides G59 - A71 and M88 - D102 of retinol binding protein;
- (e) an antisense molecule capable of inhibiting the expression of retinol binding protein receptor;
- (f) an antisense RNA, an antisense DNA, an antisense oligonucleotide;
- (g) carboxoxolone, phenylarsine oxide, citral, 3,7-dimethyl-2,6-octadienal, 4-methylpyrazole and disulphiram.

9. A method of treating a patient suffering from a hyperproliferative disorder or photoageing, which method comprises administering to the patient a compound capable of interfering with the biosynthesis of retinoic acid.

10. The method of claim 9, wherein the compound is capable of inhibiting the uptake of retinol into the cell, or wherein the compound is an inhibitor of an enzyme involved in the biosynthesis of retinoic acid.

11. An agent or antagonist capable of lowering the endogenous level of retinoic acid in a cell for use in a method of treating a hyperproliferative disorder or photoageing in a patient.

12. The antagonist of claim 11, wherein the antagonist is a retinol binding protein receptor antagonist.

13. The agent of claim 11, wherein the agent is an inhibitor of retinoic acid synthesis.
14. The agent or antagonist of claim 11, wherein the antagonist is capable of inhibiting uptake of a retinoic acid precursor or inhibiting biosynthesis of a retinoic acid precursor.
15. An antagonist of claim 11, which is selected from the group consisting of:
- (a) an immunoglobulin capable of binding to retinol binding protein receptor;
 - (b) a peptide comprising a sequence from a receptor binding region of retinol binding protein;
 - (c) a peptide comprising a sequence K29 - Q38, G59 - A71 or M88 - D102 of retinol binding protein;
 - (d) a peptide comprising a heterodimer consisting of peptides G59 - A71 and M88 - D102 of retinol binding protein;
 - (e) an antisense molecule capable of inhibiting the expression of retinol binding protein receptor;
 - (f) an antisense RNA, an antisense DNA, an antisense oligonucleotide;
 - (g) carbenoxolone, phenylarsine oxide, citral, 3,7-dimethyl-2,6-octadienal, 4-methylpyrazole and disulphiram.
16. The method of claim 1, wherein the hyperproliferative disorder comprises psoriasis, acne vulgaris, acne rosacea, actinic keratosis, solar keratoses, squamous carcinoma *in situ*, the ichthyoses, hyperkeratoses, disorders of keratinization such as Darriers disease, palmoplantar keratodermas, pityriasis rubra pilaris, epidermal naevoid syndromes, erythrokeratoderma variabilis, epidermolytic hyperkeratoses, non-bullous ichthyosiform erythroderma, cutaneous lupus erythematosus and lichen planus.psoriasis, acne vulgaris, or cancer.

17. The agent or antagonist of claim 11, wherein the hyperproliferative disorder comprises psoriasis, acne vulgaris, acne rosacea, actinic keratosis, solar keratoses, squamous carcinoma *in situ*, the ichthyoses, hyperkeratoses, disorders of keratinization such as Darriers disease, palmoplantar keratodermas, pityriasis rubra pilaris, epidermal naevoid syndromes,
5 erythrokeratoderma variabilis, epidermolytic hyperkeratoses, non-bullous ichthyosiform erythroderma, cutaneous lupus erythematosus and lichen planus.psoriasis, acne vulgaris, or cancer.

18. A method for identifying a compound capable of lowering the endogenous level of retinoic acid in a cell, which method comprises: contacting a cell which expresses a retinol binding protein receptor with a candidate compound, and determining whether the level of retinoic acid in said cell is lowered as a result of said contacting; or, contacting a retinol binding protein receptor, or a fragment thereof capable of binding retinol binding protein, with a candidate compound in the presence of retinol binding protein and determining whether the levels of retinol binding protein binding to the receptor are reduced; or,
10 contacting a cell with a candidate compound, and determining whether the level of retinoic acid within the cell is reduced; or exposing a cell expressing a retinol dehydrogenase to a compound and determining whether the levels of retinal within the cell are reduced.

19. The method of claim 17 wherein the compound is an antagonist of retinol binding receptor.

20. A compound or antagonist identified by the method of claim 18.

21. A method of preventing proliferation of a cell, the method comprising lowering the endogenous level or activity of retinoic acid (RA) in the cell.

22. The method of claim 21, wherein the cell is a hyperproliferative cell.

23. The method of claim 21, wherein the cell is contacted with a compound capable of interfering with the biosynthesis of retinoic acid.

24. The method of claim 21, wherein the method comprises inhibiting the activity of a retinol binding protein receptor of the cell.

5 25. The method of claim 21, wherein the cell is contacted with an antagonist of a retinol binding protein receptor.

26. The method of claim 21, wherein the cell is contacted with an antagonist of one or more elements of a pathway which leads to biosynthesis of retinoic acid.

27. The method of claim 21, which results in cell differentiation.

10 28. A method of activating a differentiation program in a cell, the method comprising contacting the cell with a compound capable of interfering with the biosynthesis of retinoic acid.

15 29. A method of treating or alleviating the symptoms of a patient suffering from a disease, disorder, or condition, wherein the method comprises reducing the endogenous level or activity of Retinoic Acid (RA) in a cell of the patient.

30. The method of claim 29, wherein the disorder is a retinoid sensitive disorder treatable by administration of retinoids, or wherein the disorder corresponds to a side effect of administration of pharmacological levels of retinoid.

31. The method of claim 30, wherein the retinoid sensitive disorder is a disorder which is treated or whose symptoms are alleviated by administration of higher than physiological levels of retinoid to the patient.

32. The method of claim 29 wherein the disease is characterised by ectopic, over- or otherwise abnormal expression of a retinoic acid receptor response element (RARE) responsive gene, a vitamin D response element (VDRE) responsive gene, a thyroid hormone receptor response element responsive gene or a peroxisome proliferator-activated receptor (PPAR) response element responsive gene.

33. The method of claim 29, wherein the disease is characterised by an imbalance between proliferation and differentiation.

34. The method of claim 29, the method further comprising inhibiting the activity of a retinol binding protein receptor in cells of the patient, and/or inhibiting the biosynthesis of retinoic acid in the cells of the patient.

35. A pharmaceutical composition suitable for treating a patient suffering from a hyperproliferative disorder or photoageing, comprising a therapeutically effective amount of a compound or agent, together with a pharmaceutically acceptable carrier or diluent.

36. The pharmaceutical composition of claim 35, wherein the compound or agent is capable of reducing the endogenous level of retinoic acid in a cell.

37. The pharmaceutical composition of claim 35, wherein the compound or agent is a retinol uptake inhibitor.

38. The pharmaceutical composition of claim 35, wherein the compound or agent is a retinoic acid synthesis inhibitor.
39. The method of claim 29, wherein the disease, disorder or condition is selected from the group consisting of: Viral infection, HPV, HIV, HSV, HCV infection, warts, post-operative scarring, hypertrophic and keloid scarring, a disorder of melanogenesis, a disorder of pigmentation, enhanced or compromised epidermal barrier function, a disorder of bone growth, bone fracture, osteoporosis, hyperlipidaemia, hepatotoxicity, cirrhosis, hepatitis infection, cutaneous irritation, alopecia, a disorder of fertility, a disorder of spermatogenesis, a disorder of egg implantation, depression, seasonal affective disorder, atherosclerosis and a disorder of angiogenesis.